



TITLE: Short- and Long-Term Use of Benzodiazepines in Patients with Generalized Anxiety Disorder: A Review of Guidelines

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CONTEXT AND POLICY ISSUES

Generalized anxiety disorder (GAD) is a chronic and disabling disorder that is primarily characterized by excessive anxiety and uncontrollable worry about everyday life.^{1,2} In addition to this worry, the patient must also present with three out of the following six symptoms for a definitive diagnosis: restlessness, difficulty concentrating, sleep disturbances, irritability, muscle tension, and becoming easily fatigued.¹ Patients with GAD are often functionally impaired and can be significantly distressed due to their symptoms.² The onset of GAD tends to be gradual in nature, it can fluctuate in severity, and is generally both recurrent and chronic.² According to the International Psychopharmacology Algorithm Project (IPAP), GAD's 12-month prevalence ranges between 1.1 and 3.6% while its lifetime prevalence is estimated to range between 4.1 and 6.6%.² GAD is approximately twice as predominant in women than men, is commonly diagnosed in middle age, and is also commonly seen in the elderly (estimated up to between 7.3%¹ and 10.2%² of this population).¹ While GAD has been observed in childhood and adolescence, it is not thought to be this population's most prominent anxiety disorder.³ While GAD can be a pure and singular disorder⁴ it is most often observed alongside other co-morbid conditions such as panic disorder, health anxiety, obsessive-compulsive disorder, major depression, and phobic anxiety disorders.⁵ GAD is associated with using a large proportion of health services as it is one of the most common mental health disorders encountered in primary medical care.⁵

A treatment plan for GAD aims to accomplish the following aspects:

- Reduce both the psychic (i.e. worry and anxiety) and somatic symptoms,
- Treat the co-morbid conditions,
- Improve the patient's quality of life and functionality,
- To continue treatment until remission and to prevent relapse.¹

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The mainstay of GAD treatment involves pharmacologic treatment but can also consist of psychological treatment (i.e. cognitive behavioural therapy).¹ First-line pharmacological treatment involves either the selective serotonin reuptake inhibitors (SSRIs) or the selective norepinephrine/noradrenaline reuptake inhibitors (SNRIs).² While these are the most effective treatments, they can produce adverse events and they also have a slower onset of action, during which there may be an increase in anxiety.⁶ Benzodiazepines (BZDs) are a class of drug that is presumed to indirectly promote gamma-amino butyric acid (GABA) activity and rapidly control the core symptoms associated with GAD.¹ They have been historically effective when used in the short-term treatment of GAD but have to be used with caution due to their adverse effect profile such as drowsiness, falls, confusion, impairment of memory, and incoordination (which can be particularly problematic in the elderly), their tendency for dependence, and potential for substance abuse.¹ For these reasons and to determine their appropriate use, this report will review the evidence for the short- and long-term use of BZDs for the treatment of GAD.

RESEARCH QUESTION

What are the guidelines associated with the short- and long-term use of benzodiazepines for patients with generalized anxiety disorder (GAD)?

KEY FINDINGS

The short-term use of benzodiazepines for the treatment of generalized anxiety disorder is recommended as adjunctive therapy to antidepressants until their effectiveness is apparent or in times of acute crisis or increased anxiety. One guideline specified a daily dosage of alprazolam ranging between 1.5 mg and 6 mg when used to control the anxiety associated with first-line use of antidepressants. Long-term use of benzodiazepines is only recommended in patients who do not respond to or cannot tolerate numerous first-line therapies. No recommendations were provided on the maximum daily doses for long-term BZD treatment for GAD. For special populations, the guidelines generally advise against the use of BZDs in the elderly (or to use at lower adult doses if required), to use them sparingly in children and adolescents, and to use them with caution during the first and third trimesters of pregnancy, during labour and delivery, and when breastfeeding.

METHODS

Literature Search Strategy

A limited literature search was conducted on key resources including PubMed, The Cochrane Library (2014, Issue 6), University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses and guidelines. The results of a focused search (with main concepts appearing in title or major subject heading) were also included. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and June 27, 2014, except for Canadian guidelines where the date limit was extended to ten years.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final article selection was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria	
Population	Adults and children with Generalized Anxiety Disorder (GAD)
Intervention	<ul style="list-style-type: none"> Benzodiazepines (whole drug class) as monotherapy or adjunctive therapy with selective serotonin reuptake inhibitors (SSRIs) or selective norepinephrine/noradrenaline reuptake inhibitors (SNRIs) or, Benzodiazepines as second-line therapy after failure on an SNRI or SSRI due to intolerance or inadequate response
Comparator	None
Outcomes	<ul style="list-style-type: none"> Guidelines Clinical benefit Safety (e.g. dependence or tolerance) Appropriate use
Study Designs	Health technology assessments, systematic reviews, meta-analyses, and evidence-based guidelines

Exclusion Criteria

Studies were excluded if they did not satisfy the selection criteria, if they were duplicate publications, or were published prior to January 1, 2009 (with the exception of evidence-based Canadian guidelines whereby they were only excluded if they were prior to January 1, 2004). Health technology assessments, meta-analyses, systematic reviews (SR), and evidence-based guidelines were excluded if there was incomplete reporting of methods or if they were superseded by a more recent or more rigorous review.

Critical Appraisal of Individual Studies

Key methodological aspects relevant to each study design were appraised and summarized narratively. The AMSTAR tool⁷ was used to guide the critical appraisal of the methodological quality of the SRs included in this report. Emphasis was placed upon the methods used to conduct the literature search, study selection, quality assessment, data extraction, and conflict of interest declaration. The AGREE II instrument⁸ was used to guide the critical appraisal of the evidence-based guidelines and focused on the following domains: scope and purpose, stakeholder involvement, rigor of development, clarity and presentation, applicability, and editorial independence.

SUMMARY OF EVIDENCE

Quantity of Research Available

The literature search identified a total of 316 citations. Of these, 306 citations were excluded during the title and abstract screening and ten potentially relevant articles were retrieved for full-text review. In addition, 6 potentially relevant reports were retrieved by a literature search from other sources (i.e. grey literature). Six studies were included in the review including two SRs and four evidence-based guidelines.

A PRISMA diagram demonstrating the study selection process is presented in Appendix 1.

Additional references that did not meet the selection criteria but may be of potential interest are provided in Appendix 2.

Summary of Study Characteristics

Systematic Reviews

Two SRs^{3,9} were included in this review and originated from Italy⁹ and the United Kingdom.³ The 2013 Offidani et al. SR⁹ focused on the clinical effectiveness of antidepressants versus BZDs for the treatment of anxiety disorders in adults. Twenty-two RCTs (published between 1983 and 1999) were included with most (18/22) including analyses on the tricyclic antidepressants (TCA) compared with BZDs in various anxiety disorders. Studies that examined GAD (N = 3) were critically appraised and summarized separately from those that were included in a meta-analysis (involving 10 studies) for the treatment of panic disorder. The Ipser et al. 2009 SR³ focused on the efficacy and tolerability of pharmacological treatment for anxiety disorders in children and adolescents. Twenty-two short-term (≤ 16 weeks) RCTs (published from 1980 to 2008) were included in the SR and included a total of 2,519 participants. Two of the included RCTs examined the efficacy of BZDs compared to placebo and these contained mixed populations of patients with a variety of anxiety disorders.

Detailed characteristics of the SRs are provided in Appendix 3, Table 2. A detailed summary of the SR's findings are provided in Appendix 4, Table 3.

Evidence-Based Guidelines

Four evidence-based guidelines^{5,6,10,11} were included in this review and were published in 2014,⁵ 2013,¹⁰ 2011¹² (amended from the 2004 guidelines¹¹), and 2006.⁶ The recommendations focused on the pharmacological treatment of either GAD specifically,¹⁰ GAD and panic disorder (with or without agoraphobia),¹² or a variety of anxiety disorders.^{5,6} While all examined adult populations,^{5,6,10,12} those produced from the British Association for Psychopharmacology⁵ and the Canadian Psychiatric Association⁶ included pharmacological recommendations and discussions for pregnant women, children and adolescents, and the elderly. All of the guidelines provided recommendations on appropriate first-, second-, and third-line treatments, subsequently including evidence on the appropriateness of SSRIs, SNRIs, BZDs, and TCAs.^{5,6,10,12} While the guidelines mainly focused on the evidence for SSRIs and SNRIs, recommendations for BZD use were provided; albeit from a smaller evidence base.

Summary of levels of evidence and strengths of recommendations are provided in Appendix 5, Table 4. Detailed verbatim recommendations from the included guidelines are provided in Appendix 6, Table 5.

Summary of Critical Appraisal

Systematic Reviews

Both SRs^{3,9} reported rigorous methodology that included clearly described *a priori* inclusion criteria, comprehensive literature searches, duplicate data selection and data extractions (with both critical appraisal's indicating that some studies had mixtures of populations) using a two-author system, and conflict of interest declarations. While both SRs provided a list of included studies,^{3,9} only that of Ipser et al.³ also provided a list of excluded studies. In addition, both SRs^{3,9} also included analysis of heterogeneity and publication bias whereby heterogeneity between trials was reported in both SRs and publication bias did not appear to be an issue. Information from the three individual RCTs that examined pharmacotherapy in GAD was summarized and appraised in Offidani et al.⁹ but there were not enough studies to perform a meta-analysis on this indication. Ipser et al.³ also did not identify many good quality RCTs in its analysis of BZDs for the treatment of GAD and subsequently only summarized the information from two relevant RCTs, both of which contained patients with many different types of anxiety disorders.

Evidence-Based Guidelines

All four of the guidelines^{5,6,10,11} were developed by reviewing the relevant original literature, while only NICE guidelines performed a full systematic review.¹² The British Association for Psychopharmacology⁵ did not perform a systematic review but provided logistical reasons for not being able to as there was too much data from all of the primary data sources. The Canadian Psychiatric Association⁶ and Bandelow et al.¹⁰ performed reviews that were "intensive" or selective, respectively, in which pertinent evidence may not have been identified. The method used to assess the quality of evidence for studies included in the Bandelow et al.¹⁰ guidelines was described as those from the Scottish Intercollegiate Guidelines Network (SIGN) but specifics were not provided. In addition, there was no grading provided for the recommendations.¹⁰ Specific scales were used to assess the quality of included evidence in the guidelines from the British Association of Psychopharmacology,⁵ the Canadian Psychiatric Association,⁶ and NICE;¹² however, NICE was the only guideline out of these three that did not present a grading system for their recommendations, with the strength of each recommendation reflected in the wording.¹² While most of the guidelines provided clearly described objectives and clinical questions,^{5,6,12} those from Bandelow et al.¹⁰ were lacking in this respect. In addition, the methods of formulating the recommendations were also not provided for Bandelow et al.,¹⁰ it was unclear if the guidelines were peer reviewed (this was also the case in those from the British Association of Psychopharmacology⁵), and there was no discussion surrounding who was involved in formulating the recommendations.¹⁰ The other three guidelines^{5,6,12} provided information on those involved in producing the guidelines; however, only experts were involved in forming guidelines from the Canadian Psychiatric Association⁶ while the other two^{5,12} additionally sought patient views and preferences.

Details of the critical appraisal for all included SRs and evidence-based guidelines are provided in Appendix 7, Table 6.

Summary of Findings

Systematic Reviews

The SRs^{3,9} included in this review were faced with a paucity of evidence (especially placebo controlled evidence) regarding the use of BZDs for the treatment of GAD in adults⁹ or in children and adolescents.³ For this reason and for concerns relating to their potential dependency and associated adverse event profiles, Ipser et al.³ were unable to recommend and only advise against the routine use of BZDs for the treatment of any anxiety disorder in a younger (≤ 18 years of age) population. Offidani et al.⁹ also faced a paucity of controlled evidence relating to the comparison of antidepressants with BZDs for the treatment of anxiety disorders in adults. Superior efficacy or tolerability of the TCA class was not demonstrated over the BZDs for the treatment of GAD in the few trials (N=3) included in their analysis.⁹ Interestingly, TCAs were found to be less efficacious with more tolerability issues when compared with BZDs in a meta-analysis of studies looking at the treatment of panic disorder (with or without agoraphobia);⁹ however, due to the differences in these disorders, these results cannot be generalized to the GAD population. In addition to the TCA evidence, the few trials that included analyses on newer antidepressants (i.e. venlafaxine and paroxetine) did not find any significant differences in treatment response when compared with BZD use and there were more discontinuations due to adverse events observed in the venlafaxine group.⁹ Specific findings of the SRs^{3,9} included in this review are provided in Appendix 4, Table 3.

Evidence-Based Guidelines

Many consistent recommendations were observed across the evidence-based guidelines identified in this review.^{5,6,10,12} One identical recommendation in all of the guidelines included the use of BZDs for acute treatment in patients with GAD,^{5,6,10,12} whether it be as adjunctive treatment to an antidepressant (until the full effect of the antidepressant is apparent),¹⁰ as a short-term measure in a crisis,^{6,12} or simply in the acute phase of treatment (i.e. usually about four to eight weeks).⁵ As a caveat to using BZDs for the acute treatment of patients with GAD, the British Association for Psychopharmacology also indicated that medications should be used alongside psychological treatment (e.g. either cognitive behavioural therapy or applied relaxation).⁵ The NICE guidelines¹² were the only guidelines that did not suggest any further use of BZDs outside of acute treatment in a crisis or high anxiety situation. In all guidelines, clinical judgment, treatment response, susceptibility for abuse, and the side effect profile were necessary when determining if BZDs were appropriate for specific lines of treatment and populations.^{5,6,10,12}

While BZDs are predominantly recommended in short-term acute treatment, the Canadian Psychiatric Association,⁶ the British Association for Psychopharmacology,⁵ and the guidelines from Bandelow et al.¹⁰ also specified that BZDs (alprazolam, bromazepam, diazepam, and lorazepam mentioned specifically⁶) were a second-line treatment option in patients with GAD^{5,6,10}. Only the NICE guidelines did not specifically recommend BZDs for second line treatment. Doses were not provided for GAD treatment in most of the identified guidelines with the exception of those from Bandelow et al.¹⁰ whereby alprazolam at a dose of 1.5 mg to 6 mg

(usually 3 mg) was appropriate when used short-term as concomitant treatment to an antidepressant.

Short-term treatment is the principal recommendation for the BZD class in GAD however long-term use can be considered in patients who remain unresponsive to a succession of treatments (including both drug and psychological) or who experience intolerance.^{5,10} The Canadian Psychological Association echoed this recommendation⁶ but did not include prerequisite conditions like those from the British Association for Psychopharmacology⁵ and Bandelow et al.¹⁰ One noteworthy aspect in all of the guidelines that supported the long-term use of BZDs was the lack of a definition of the duration of “long-term use.”^{5,6,10}

Special populations were also considered in the discussions surrounding the appropriateness of BZDs for the treatment of GAD. Due to the paucity of evidence and concerns regarding the potential for side effects and dependence, BZDs (of which only alprazolam was specifically mentioned) were recommended to be used sparingly in children and adolescents in one guideline.⁶ Elderly patients are more susceptible to both the therapeutic and toxic effects of BZDs, hence avoidance of this class of drug or usage at low dosages was advised.⁶ Caution for the use of BZDs was also recommended in women who were either pregnant (first and third trimesters or during labour and delivery) or breastfeeding; however, this advice was presented in generalities and not specific to women suffering from GAD.⁶ The aforementioned populations were also mentioned in the guidelines from the British Association for Psychopharmacology; however, no specific guidance was provided regarding BZDs and options were also presented as generalities.⁵

Specific BZDs drugs that have been examined in clinical trials for the treatment of anxiety disorders include alprazolam,^{5,6} diazepam,^{5,6} lorazepam,^{5,6} bromazepam,^{5,6} and clonazepam.⁶ Of these medications, RCT evidence and subsequent recommendations for use are available that indicated the effectiveness of alprazolam, bromazepam, lorazepam, and diazepam for the treatment of GAD.⁶

A summary of the recommendations plus additional notes of interest for BZD use in GAD is presented in Appendix 8, Table 7. Specific verbatim recommendations are provided in Appendix 6, Table 5.

Limitations

The NICE guidelines¹² were the only ones whose evidence was backed by a full systematic review. Therefore, there remains the distinct possibility that the guidelines produced by the British Association for Psychopharmacology,⁵ the Canadian Psychiatric Association,⁶ and Bandelow et al.¹⁰ may not have considered some relevant evidence.

While there were sections in each of the guidelines specific to the treatment of GAD with BZDs, many of the recommendations produced were provided as generalities. These discussions centered on the general use of BZDs or other medications for anxiety disorders, on the screening and diagnosis of GAD, or on the full spectrum of treatment (both drug and psychological) for GAD. Therefore, one must sort through the numerous recommendations to find specifics on the use of BZDs for the treatment of GAD. While this is indeed a strength regarding the comprehensiveness of the recommendations, it is a limitation when trying to find specific details or items of interest. In addition, of the guidelines that discussed BZDs in special populations,^{5,6} neither produced specific recommendations either for or against their use.

Therefore, it remains up to the discretion of the physician on how to apply this information when confronted with a patient belonging to one of these populations.

Only one guideline provided information on appropriate dosages for acute treatment¹⁰ while none^{5,6,10,12} provided dosing (either maximum or otherwise) for the use of BZDs in long-term or acute crises situations. The Canadian Psychiatric Association did provide BZD-specific daily and maximum dosing provided from Health Canada; however, it was noted that these doses were appropriate for healthy individuals and not necessarily those with anxiety disorders.⁶ Therefore, the applicability of dosing in patients with GAD is still up to the discretion of the physician.

Even though the methodological quality of the SRs included in this review was high, the paucity of evidence on the use of BZDs for the treatment of GAD in adults⁹ or children and adolescents³ hindered the author's ability to draw firm conclusions regarding BZD use. There remains a need to further examine the use of BZDs particularly in children and adolescents. In addition, the evidence that met the inclusion criteria for both of the SRs^{3,9} came from trials with mixed population of patients with a variety of anxiety disorders; hence the evidence may not have been generalizable to patients diagnosed with GAD.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

Recommendations on the use of BZDs for the short-term^{5,6,10,12} and long-term^{5,6,10} treatment of GAD were summarized in four evidence-based guidelines. BZDs were unanimously recommended for acute treatment of GAD^{5,6,10,11} either concomitantly until the effects of the antidepressant were apparent¹⁰ or as a short-term measure during a crisis or times of increased anxiety.^{6,12} In addition to this, the British Association for Psychopharmacology also indicated that medications should be used alongside psychological treatment (either cognitive behavioural therapy or applied relaxation).⁵ Daily maximum doses for acute treatment were only provided in the guidelines from Bandelow et al.¹⁰ whereby alprazolam was recommended at a dose between 1.5 mg to 6 mg when used adjunctively with an antidepressant. Additional recommendations on dosing were provided in the 2008 WFSBP guidelines, upon which the Bandelow guideline was based, and included the use of diazepam and lorazepam for the treatment of GAD at adult daily doses of 5 to 15 mg and 2 to 8 mg, respectively. These guidelines, however, did not meet the inclusion criteria for the current review (outside of date range). Long-term treatment of GAD with BZDs was only recommended for patients experiencing a lack of treatment response or intolerance to preceding first-line antidepressants⁶ and psychological treatments.^{5,10} No maximum doses for long-term BZD-treatment were provided. While recommendations were not specifically made for or against the use of BZDs to treat GAD in the elderly, children and adolescents, and pregnant and breastfeeding women, discussions surrounding their appropriate use were provided. BZDs were advised either to be avoided or used at lower dosages in the elderly, used sparingly in children and adolescents, and used with caution in the first and third trimesters of pregnancy, during labour and delivery, and while breastfeeding.⁶

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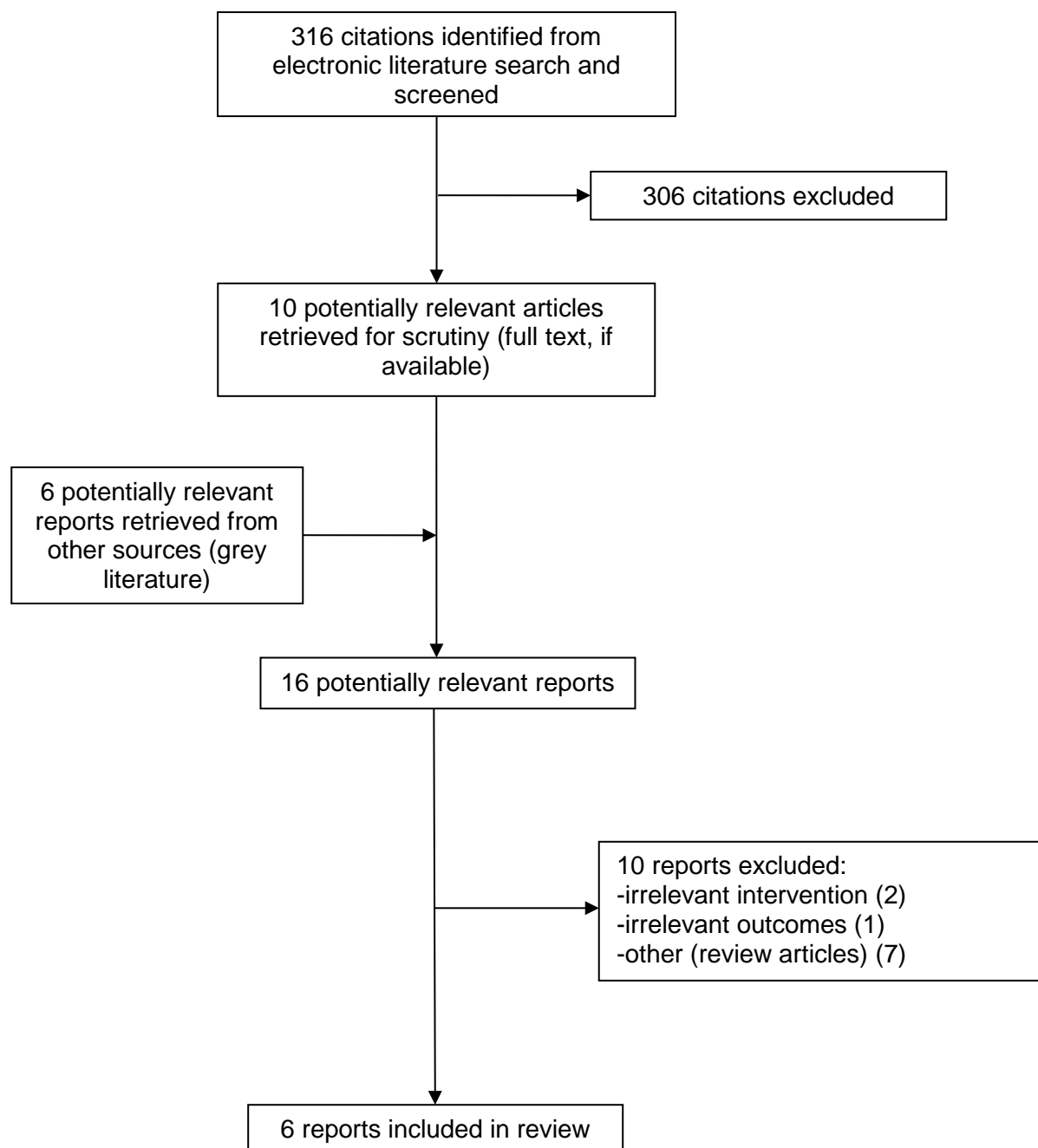
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12. National Institute for Health and Clinical Excellence, National Collaborating Centre for Mental Health. Anxiety disorder in adults: The NICE guideline on management in primary, secondary and community care [Internet]. London: The British Psychological Society and The Royal College of Psychiatrists; 2011. [cited 2014 Jul 22]. (National Clinical Guideline Number 113). Available from: <http://www.nice.org.uk/guidance/cg113/resources/anxiety-full-guidance3>

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Additional Articles of Potential Interest

Review Articles

Reinhold JA, Mandos LA, Rickels K, Lohoff FW. Pharmacological treatment of generalized anxiety disorder. *Expert Opin Pharmacother*. 2011 Nov;12(16):2457-67.

[PubMed: PM21950420](#)

el-Guebaly N, Sareen J, Stein MB. Are there guidelines for the responsible prescription of benzodiazepines? *Can J Psychiatry*. 2010 Nov;55(11):709-14.

[PubMed: PM21070698](#)

Ballenger JC, Davidson JR, Lecrubier Y, Nutt DJ, Borkovec TD, Rickels K, et al. Consensus statement on generalized anxiety disorder from the International Consensus Group on Depression and Anxiety. *J Clin Psychiatry*. 2001;62 Suppl 11:53-8.

[PubMed: PM11414552](#)

Evidence-Based Guidelines and Recommendations (outside of inclusion criteria date range)

Guideline Development Group on Treatment of Patients with Anxiety Disorders in Primary Care. Clinical practice guideline for treatment of patients with anxiety disorders in primary care [Internet]. Madrid: National Plan for the NHS of the MSC. Health Technology Assessment Unit; 2008. [cited 2014 Jul 28]. Available from:

http://www.guiasalud.es/GPC/GPC_430_Anxiety_Lain_Entr_compl_en.pdf

Clinical Practice Guidelines/Algorithms – Uncertain Methodology

Guidelines & Protocols Advisory Committee. Anxiety and depression in children and youth - diagnosis and treatment [Internet]. Victoria (BC): British Columbia. Ministry of Health Services; 2010 Jan 1. [cited 2014 Jul 28]. Available from: <http://www.bcguidelines.ca/pdf/depressyouth.pdf>

Generalised anxiety disorder in adults. *Best Practice Journal* [Internet]. 2009 Dec 25 [cited 2014 Jul 28];(25):20-7. Available from:

http://www.bpac.org.nz/BPJ/2009/December/docs/bpj25_anxiety_pages20-27.pdf

Which treatment for what anxiety disorder? *National Prescribing Service Newsletter* [Internet]. 2009 [cited 2014 Jul 28];(65). Available from:

http://www.nps.org.au/data/assets/pdf_file/0003/76827/News65_anxiety_1009.pdf

APPENDIX 3: Characteristics of Included Systematic Reviews

Table 2: Summary of Systematic Review Characteristics		
Author, Year, Country	Trial Characteristics	Outcomes
Offidani et al., ⁹ 2013, Italy and US	<ul style="list-style-type: none"> Search period up to December 2012 22 studies included <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Published RCTs comparing BZD and antidepressants in the treatment of adults (≥ 18 years of age) with anxiety disorders 	<p>Primary Outcomes:</p> <ul style="list-style-type: none"> Response rates as defined by the study investigators <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> Dropout rates AEs
Ipser et al., ³ 2009, UK	<ul style="list-style-type: none"> Search period up to August 2008 22 short term (≤16 weeks) RCTs included <p>Inclusion criteria:</p> <ul style="list-style-type: none"> Published and unpublished RCTs (cross-over, parallel-group and cluster randomized trials included) Children/adolescents (≤ 18 years of age) diagnosed with anxiety disorders according to DSM-III, DSM-III-R, and DSM-IV Includes anxiety disorders traditionally regard as adult disorders (panic disorder with or without agoraphobia, GAD, social phobia, OCD, and post-traumatic and acute stress disorder) N = 2519 <p>Specific to BZDs:</p> <ul style="list-style-type: none"> N = 2 trials; 1 trial included alprazolam treatment (not treating GAD); 1 trial included clonazepam treatment (mixed indication population) 	<p>Primary Outcomes:</p> <ul style="list-style-type: none"> Treatment response (number of responders) using: <ul style="list-style-type: none"> CGI-I Summary statics from closely related measure (CGI-SP) Anxiety symptoms and symptom cluster response using: <ul style="list-style-type: none"> PARS CY-BOCS <p>Secondary Outcomes:</p> <ul style="list-style-type: none"> Response of comorbid symptoms (Childhood Depression Rating Scale) QoL and functional disability measures Medication acceptability (those who withdrew due to treatment emergent AEs) Significant differences between medications and control groups in common drug-related AEs prevalence (≥ 10%) Comparison of relapse

AE = adverse event; BZD = benzodiazepines; CGI-I = Clinical Global Impressions scale; CGI-SP = Clinical Global Impressions scale for Social Phobia; CY-BOCS = Child Yale-Brown Obsessive-Compulsive Scale; DSM = Diagnostic and Statistical Manual of Mental Disorders; GAD = generalized anxiety disorder; NR = not reported; OCD = obsessive-compulsive disorder; PARS = Pediatric Anxiety Rating Scale; QoL = quality of life; RCT = randomized controlled trials; UK = United Kingdom.

APPENDIX 4: Summary of Clinical Findings from Systematic Reviews

Table 3: Summary of Findings and Authors' Conclusions Specific to Benzodiazepines		
Author, Year, Country	Main Study Findings	Authors' Conclusions
Offidani et al., ⁹ 2013, Italy	<ul style="list-style-type: none"> No significant differences in treatment response between either venlafaxine XR (75 and 150 mg/day) or paroxetine (20 mg/day) and the BZDs diazepam (5 mg/day) and lorazepam (1.5 mg/day) in patients with GAD. Increased discontinuations due to AEs were observed in patients taking venlafaxine when compared to diazepam (1 RCT, N = 540; patients with GAD). Somatic symptoms significantly improved in patients taking lorazepam when compared to paroxetine or placebo (1 RCT, N = 169; patients with GAD). 	<ul style="list-style-type: none"> "Our systematic review found a paucity of studies providing a controlled direct comparison of AD and BDZ in anxiety disorders." page 359 "The superiority of AD over BDZ in terms of efficacy and tolerability was not supported by the available evidence." page 359 "Overall, in GAD, complex phobias and mixed anxiety-depressive disorders, BDZ were better tolerated than both TCA and newer antidepressants, leading to fewer dropouts and adverse reactions." page 360
Ipser et al., ³ 2009, UK	<ul style="list-style-type: none"> Increase in the use of BZDs is not recommended for the pediatric population. The RCT (Graae, 1994^a) contained a population with a mixture of indications treated with clonazepam; no significant information on side effects ($p < 0.1$). The final dosage in the Graae, 1994 trial was 0.25 mg/d – 2 mg/d. Frequent AEs included drowsiness, irritability, and oppositional behaviour when treating a variety of anxiety disorders. 2 children on clonazepam withdrew due to serious disinhibition, marked irritability, tantrums, and aggressive behaviour. 	<ul style="list-style-type: none"> "The routine use of benzodiazepines cannot be recommended, as there is insufficient efficacy data from controlled trials to offset potential adverse effects of this agent." page 16.

AE = adverse event; BZD = benzodiazepine; RCT = randomized controlled trial; TCA = tricyclic antidepressants.

^a The trial was a double blind RCT, placebo-controlled, crossover, flexible dose with no washout with unclear blinding, allocation concealment, and randomization. In addition, they included a mix of disorders with unclear morbidities, the intervention was clonazepam for 8 weeks, and the dropout rate for the clonazepam group was 3 compared to 0 in the placebo group.

APPENDIX 5: Summary of Guideline Evidence Levels and Strength of Recommendations

Table 4: Levels of Evidence and Grading of Recommendations^a

Guideline/Author, Year, Country	Quality or Level of Evidence	Grading/Strength of Recommendation
BAP, ⁵ 2014, UK	<p><i>Categories of evidence relevant to treatment:</i></p> <p>I [M] - Evidence from meta-analysis of randomized double-blind placebo-controlled trials.</p> <p>I [PCT] - Evidence from at least one randomized double-blind placebo-controlled trial.</p> <p>II - Evidence from at least one randomized double-blind comparator-controlled trial (without placebo).</p> <p>III - Evidence from non-experimental descriptive studies.</p> <p>IV - Evidence from expert committee reports or opinions and/or clinical experience of respected authorities.</p> <p><i>Categories of evidence relevant to observational findings and associations:</i></p> <p>I - Evidence from large representative population samples.</p> <p>II - Evidence from small, well designed but not necessarily representative samples.</p> <p>III - Evidence from non-representative surveys, case reports.</p> <p>IV - Evidence from expert committee reports or opinions and/or clinical experience of respected authorities.</p>	<p>A - Directly based on category I evidence (either I [M] or I [PCT]).</p> <p>B - Directly based on category II evidence or an extrapolated recommendation from category I evidence.</p> <p>C - Directly based on category III evidence or an extrapolated recommendation from category I or II evidence.</p> <p>D - Directly based on category IV evidence or an extrapolated recommendation from other categories.</p> <p>S - Standard of clinical care.</p>
Bandelow et al., ¹⁰ 2013, Germany ^b	<p><i>Assessment of levels based on SIGN protocol:</i></p> <p>1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.</p> <p>1+ Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.</p>	NR

Table 4: Levels of Evidence and Grading of Recommendations^a

Guideline/Author, Year, Country	Quality or Level of Evidence	Grading/Strength of Recommendation
	<p>1 - Meta-analyses, systematic reviews, or RCTs with a high risk of bias.</p> <p>2++ High quality systematic reviews of case control or cohort studies.</p> <ul style="list-style-type: none"> High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal. <p>2+ Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.</p> <p>2 - Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.</p> <p>3 Non-analytic studies, eg case reports, case series.</p> <p>4 Expert opinion.</p>	
NICE, ¹² 2011, UK	<p><i>Quality of evidence:</i>¹¹</p> <p>High - Further research is very unlikely to change our confidence in the estimate of the effect.</p> <p>Moderate - Further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate.</p> <p>Low - Further research is very likely to have an important impact on our confidence in the estimate of the effect and is likely to change the estimate.</p> <p>Very low - Any estimate of effect is very uncertain.</p>	The strength of each recommendation was reflected in the wording of the recommendation, rather than by using labels or symbols.

Table 4: Levels of Evidence and Grading of Recommendations^a

Guideline/Author, Year, Country	Quality or Level of Evidence	Grading/Strength of Recommendation
	<p><i>Overall assessment of the paper:</i></p> <p>++ - All or most of the criteria have been fulfilled. Where they have not been fulfilled, the conclusions of the study or review are thought very unlikely to alter the conclusions.</p> <p>+ - Some of the criteria have been fulfilled. Those criteria that have not been fulfilled or not adequately described are thought unlikely to alter the conclusions.</p> <p>- - Few or no criteria fulfilled. The conclusions of the study are thought likely or very likely to alter the conclusions.</p>	
CPA, ⁶ 2006, Canada	<p>1 – Meta-analysis or replicated RCT that includes a placebo condition.</p> <p>2 – At least one RCT with placebo or active comparison condition.</p> <p>3 – Uncontrolled trial with at least 10 or more subjects.</p> <p>4 – Anecdotal reports or expert opinion.</p>	<p>First-line – Level 1 or Level 2 evidence plus clinical support for efficacy and safety.</p> <p>Second-line – Level 3 evidence or higher plus clinical support for efficacy and safety.</p> <p>Third-line – Level 4 evidence or higher plus clinical support for efficacy and safety.</p> <p>Not recommended – Level 1 or Level 2 evidence for lack of efficacy.</p>

BAP = British Association for Psychopharmacology; CPA = Canadian Psychiatric Association; M = meta-analysis; NICE = National Institute for Health and Clinical Excellence; NR = not reported; PCT = placebo-controlled trial; QRS = Quality of Research; SIGN = Scottish Intercollegiate Guidelines Network; UK = United Kingdom.

^a Verbatim from the guidelines.

^b Structured evaluation performed according to the SIGN recommendations.

APPENDIX 6: Guidelines and Recommendations for Benzodiazepine Treatment in GAD

Table 5: Guidelines and Recommendations	
Guideline/Author, Year, Country	Recommendations
BAP, ⁵ 2014, UK	<p>Deciding when and which treatment is required:</p> <ul style="list-style-type: none"> “The choice of a particular treatment should be influenced by the supporting evidence base, by clinical characteristics (such as treatment contraindications and expected impact of potential side effects), the preferences of patients, personal experience, and the local availability of any proposed intervention.[S]” page 8 <p>General aspects of pharmacological treatment:</p> <ul style="list-style-type: none"> “Discuss the anticipated balance of potential benefits and potential risks of specific psychotropic medications with patients before stating treatment.[S]” “Remain familiar with the evidence base for other classes of medication, as many patients do not respond to or are intolerant of SSRI treatment, but may respond to other classes of psychotropic drug. [S]” “Discuss potential adverse effects early in treatment, including increased nervousness, worsened agitation, and review patient progress carefully over the first few weeks of treatment.[A]” “Remember that benzodiazepines can be effective in many patients with anxiety disorders [A], but recognise that their use should generally only be short-term: and only considered beyond this in patients who have not responded to a succession of other treatment approaches.[S]” “Discuss the potential for experiencing discontinuation or withdrawal symptoms during unforeseen abrupt interruptions to treatment and after the planned end of pharmacological treatment.[S]” pages 10-11 <p>Managing patients with generalized anxiety disorder:</p> <p>Acute treatment:</p> <ul style="list-style-type: none"> “Choose an evidence-based acute treatment [A] <ul style="list-style-type: none"> pharmacological: most SSRIs (citalopram, escitalopram, paroxetine, sertraline), duloxetine, venlafaxine, pregabalin, agomelatine, quetiapine, some benzodiazepines (alprazolam, diazepam, lorazepam), imipramine, buspirone, hydroxyzine and trazodone.[A] psychological: cognitive-behaviour therapy, applied relaxation.[A]” “Take account of patient clinical features, needs and preference and local service availability when choosing treatment, as pharmacological and psychological approaches have broadly similar efficacy in acute treatment. [S]” page 14 <p>When initial treatments fail:</p> <ul style="list-style-type: none"> “Consider use of benzodiazepines after a non-response to SSRI, SNRI, pregabalin and buspirone treatment.[S]” page 15

Table 5: Guidelines and Recommendations

Guideline/Author, Year, Country	Recommendations
	<p>Treatment of children and adolescents:</p> <ul style="list-style-type: none"> • <i>“Reserve pharmacological treatments for children and teenagers who have not responded to psychological interventions, and in whom the anticipated benefits are expected to outweigh any potential risks.[S]”</i> • <i>“Choose from the same range of treatments as considered for adult patients, considering an SSRI for first-line pharmacological treatment: fluoxetine may be the SSRI with the best balance of potential benefit and risk.[B]”</i> page 24 <p>Treatment in elderly and physically ill patients:</p> <ul style="list-style-type: none"> • <i>“Manage elderly patients in a broadly similar way to younger patients, being mindful of the possibility of drug interactions, the potential need for lower doses in patients with renal or hepatic impairment, and the risk of worsening any pre-existing cognitive impairment through the use of medications with sedative effects.[S]”</i> page 25 <p>Women of child-bearing age:</p> <ul style="list-style-type: none"> • <i>“Keep familiar with the changing evidence base about the potential hazards of treatment of pregnant and breast-feeding women with psychotropic drugs.[S]”</i> • <i>“Keep familiar with the changing evidence base about the potential hazards of treatment of pregnant and breast-feeding women with psychotropic drugs.[S]”</i> page 25
Bandelow et al., ¹⁰ 2013, Germany	<ul style="list-style-type: none"> • <i>“For concomitant treatment with an antidepressant until the onset of the antidepressant effect, alprazolam^a 1.5–6 mg, usually 3 mg.”^b</i> page 303
NICE, ¹² 2011, UK	<p>Drug treatment:</p> <ul style="list-style-type: none"> • <i>“Do not offer a benzodiazepine for the treatment of GAD in primary or secondary care except as a short-term measure during crises. Follow the advice in the 'British national formulary' on the use of a benzodiazepine in this context. [new 2011]”</i> • <i>“Before prescribing any medication, discuss the treatment options and any concerns the person with GAD has about taking medication. Explain fully the reasons for prescribing and provide written and verbal information on:</i> <ul style="list-style-type: none"> ○ <i>the likely benefits of different treatments.</i> ○ <i>the different propensities of each drug for side effects, withdrawal syndromes and drug interactions.</i> ○ <i>the risk of activation with SSRIs and SNRIs, with symptoms such as increased anxiety, agitation and problems sleeping.</i> ○ <i>the gradual development, over 1 week or more, of the full anxiolytic effect</i> ○ <i>the importance of taking medication as prescribed and the need to continue treatment after remission to avoid relapse. [new 2011]”</i> page 18

Table 5: Guidelines and Recommendations

Guideline/Author, Year, Country	Recommendations
CPA, ^a 2006, Canada	<ul style="list-style-type: none"> Although benzodiazepines are a second-line treatment, they may be used at any time if agitation or anxiety is severe. However they should ideally be used short-term. page 53S <p>Medications in Pregnancy:</p> <ul style="list-style-type: none"> “First trimester - Benzodiazepines can be used with caution. Third trimester and labour–delivery - High-dose benzodiazepines should be used with caution.” page 18S <p>Health Canada-approved recommended daily doses of pharmacotherapy:</p> <ul style="list-style-type: none"> “Alprazolam^c <ul style="list-style-type: none"> Initial daily dose (mg) = 0.25 Maximum daily dose (mg) = 1.5 – 3.0 Bromazepam^c <ul style="list-style-type: none"> Initial daily dose (mg) = 6 Maximum daily dose (mg) = 30 Clonazepam^c <ul style="list-style-type: none"> Initial daily dose (mg) = 0.25 Maximum daily dose (mg) = 4 Diazepam^c <ul style="list-style-type: none"> Initial daily dose (mg) = 2.5 Maximum daily dose (mg) = 10 Lorazepam^c <ul style="list-style-type: none"> Initial daily dose (mg) = 0.5 Maximum daily dose (mg) = 3-4”, page 19S <p>Strength of evidence of pharmacotherapy for GAD:</p> <ul style="list-style-type: none"> “Anxiolytics: <ul style="list-style-type: none"> Benzodiazepines <ul style="list-style-type: none"> Alprazolam – Level 1 evidence Bromazepam – Level 1 evidence Lorazepam – Level 1 evidence Diazepam – Level 1 evidence,” page 54S <p>Recommendations for pharmacotherapy for GAD:</p> <ul style="list-style-type: none"> “Second-line – Alprazolam, bromazepam, lorazepam, diazepam,” page 55S <p>Strength of evidence of treatment for anxiety disorders in children and adolescents:</p> <ul style="list-style-type: none"> “For GAD – Alprazolam (Level 2, negative),” page 68S

A = directly based on category I evidence (either I [meta-analysis] or I [placebo-controlled trials]); BAP = British Association for Psychopharmacology; GAD = generalized anxiety disorder; NICE = National Institute for Health and Clinical Excellence; S = standard of clinical care; SNRI = selective norepinephrine/noradrenaline reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors; UK = United Kingdom.

^a Alprazolam approved in Germany for the treatment of anxiety states /disorders.

^b Accompanying psychotherapy is recommended in all cases.

^c “Multiple generic and (or) brand name products; data from respective Canadian product monographs; dosages are for healthy adults, not necessarily for those with anxiety disorders.”

APPENDIX 7: Summary of Critical Appraisal

Table 6: Critical Appraisal of the Included Systematic Reviews and Evidence-Based Guidelines

Guideline/Author, Year, Country	Strengths	Limitations
<i>Systematic Reviews</i>		
Offidani et al., ⁹ 2013, Italy	<ul style="list-style-type: none"> • <i>A priori</i> inclusion criteria were established. • A comprehensive systematic review and reference list searching was used to identify relevant literature. • Duplicate study selection and data extraction were performed. • Meta-analysis was performed. • A list of included studies was provided. • Conflicts of interest were declared. • Funding disclosed. 	<ul style="list-style-type: none"> • Potential for publication bias as only English RCTs were included. • Inclusion criteria were not clearly defined. • A list of excluded studies was not provided. • Evidence primarily from a mixed population of anxiety disorders.
Ipser et al., ³ 2009, UK	<ul style="list-style-type: none"> • Research questions and inclusion criteria established <i>a priori</i>. • Comprehensive literature search with no language restrictions; additional search of ongoing trials and attempts to contact principal authors. • Duplicate study selection and extraction were performed. • Quality of trials assessed using CCDAN-QRS. • Included and excluded studies were provided. • Assessment of publication bias included. • Conflicts of interest declared. 	<ul style="list-style-type: none"> • The majority of included trials excluded patients with comorbid psychiatric disorders; thus, potentially limiting recommendations to those more representative of the general populations and less treatment-resistant. • Most of the trials assessed short-term treatment; hence, the results cannot be extrapolated to long-term treatment. • Lack of available placebo-controlled evidence for the BZD class. • Evidence available only in a mixed population (with a variety of anxiety disorders).
<i>Evidence-Based Guidelines</i>		
BAP, ⁵ 2014, UK	<ul style="list-style-type: none"> • Update of the 2005 recommendations. • Professional and patient groups were represented in the formation of the guidelines along with observers from 	<ul style="list-style-type: none"> • Literature review was not systematic; yet, reasons for not performing a full SR were provided. • Unclear if guidelines were externally reviewed.

Table 6: Critical Appraisal of the Included Systematic Reviews and Evidence-Based Guidelines

Guideline/Author, Year, Country	Strengths	Limitations
	<p>pharma.</p> <ul style="list-style-type: none"> Overall and specific objectives clearly described. Patient population and target users clearly described. SR, MA and existing guidelines were included in the development; descriptions of standards of care were provided where evidence was lacking. Methods for formulating recommendations were provided. Clear link between the recommendations and the supporting evidence. Recommendations were clearly described and specific. Algorithms and advice for treatment clearly described. Lack of funding described. 	<ul style="list-style-type: none"> Conflicts of interest statement provided but no specifics were available. List of included and excluded studies not provided.
Bandelow et al., ¹⁰ 2013, Germany ^a	<ul style="list-style-type: none"> Additional 21 studies were evaluated along with the original studies included in the 2008 WFSBP guidelines.^b Clear objectives in the revised 2008 WFSBP guidelines.^b on which these were based. Links to between the recommendations and supporting evidence provided. Conflicts of interest provided. 	<ul style="list-style-type: none"> Unclear how trial evaluations were specifically conducted using the SIGN recommendations. Unclear if recommendation grading was based on the exact method used in the original 2008 WFSBP guidelines.^b – not explicitly stated in the article. Objectives and the clinical questions were not clearly described. Methods for formulating the recommendations were not provided. Only treatments that were observed to be effective in the majority of trials where they were being studied were recommended.

Table 6: Critical Appraisal of the Included Systematic Reviews and Evidence-Based Guidelines

Guideline/Author, Year, Country	Strengths	Limitations
		<ul style="list-style-type: none"> • Populations not always specified. • No information on the development group or whether the views and preferences of patients were taken into account. • A selective, and not systematic, search was performed to identify relevant studies for inclusion. • Unclear whether recommendations were peer reviewed. • Guideline funding not specified.
NICE, ¹² 2011, UK	<ul style="list-style-type: none"> • Update of the 2009 amended guidelines - originally published in 2004. • The Guideline Development Group consisted of professionals, patients, and academic experts. • Objectives and clinical questions clearly described/presented. • Patient population and target users clearly described. • SR review used to obtain available evidence. • Methods for formulating recommendations were provided. • Clear link between the recommendations and the supporting evidence. • Externally reviewed by registered stakeholders. • Recommendations were clearly described. • The authors did indicate when a guideline was new as of 2011. 	<ul style="list-style-type: none"> • Informal consensus process was adopted to answer questions lacking high-quality evidence (i.e. opinions). • List of excluded studies not provided. • The strength of recommendations were described narratively and not with a predetermined rating scale.

Table 6: Critical Appraisal of the Included Systematic Reviews and Evidence-Based Guidelines

Guideline/Author, Year, Country	Strengths	Limitations
	<ul style="list-style-type: none"> Conflicts of interest declared. 	
CPA, ^b 2006, Canada	<ul style="list-style-type: none"> Objectives clearly described. Patient population and target users clearly described. Hand searches included to identify evidence. Methods for formulating recommendations provided. Externally reviewed by the Canadian psychiatric community. Explicit links between recommendations and supporting evidence provided. Recommendations were clearly presented. 	<ul style="list-style-type: none"> Only psychiatrists, psychologists, and a family physician were included in the working groups; no patients were included. Systematic review was not performed to identify evidence; described as an intensive review. Inclusion criteria not clearly described. Conflicts of interest not declared. No information provided on funding.

BAP = British Association for Psychopharmacology; MA = meta-analysis; NICE = National Institute for Health and Clinical Excellence; QRS = Quality of Research; RCT = randomized controlled trial; SIGN = Scottish Intercollegiate Guidelines Network; SR = systematic review; UK = United Kingdom; WFSBP = World Federation of Societies of Biological Psychiatry.

^a Critical appraisal based solely on the 2013 journal article and not on the revised 2008 guidelines by the World Federation of Societies of Biological Psychiatry.

^b Guidelines for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders.

APPENDIX 8: Recommendations and Important Notes and Advice Reported in the Evidence-Based Guidelines

Table 7: Summary of Recommendations for Benzodiazepine Use in GAD

Guideline/ Author, Year, Country	Benzodiazepine(s)	Treatment	Dose, Duration	Recommendations	Author's Additional Notes
BAP, ⁵ 2014, UK	Alprazolam, diazepam, lorazepam	Second line	<ul style="list-style-type: none"> NR NR 	<p>General aspects of pharmacological treatment:</p> <ul style="list-style-type: none"> BZDs should generally only be used short-term; however, they can be considered longer term in patients unresponsive to a succession of other treatments.^b <p>Managing Patients with GAD: Acute Treatment</p> <ul style="list-style-type: none"> Can use some BZD (alprazolam, diazepam, and lorazepam). <p>When initial treatments fail:</p> <ul style="list-style-type: none"> Can consider use of BZDs after unresponsiveness to SSRI, SNRI, and buspirone treatment. 	<p>General aspects of pharmacological treatment:</p> <ul style="list-style-type: none"> Decide when and which treatment with psychotropic drugs is necessary and use evidence base and clinical judgement (i.e. contraindications, potential side effects, patient preference, personal experience, and local availability) to determine which to choose. Remain familiar with evidence base for other classes of medications should the patients be unresponsive/intolerant to first line (SSRI) treatment. <p>Managing Patients with GAD: Acute Treatment</p> <ul style="list-style-type: none"> Use pharmacological treatment and psychological treatment (CBT or applied relaxation).
Bandelow et al., ¹⁰ 2013, Germany	Alprazolam ^a	Second line	<ul style="list-style-type: none"> 1.5 – 6 mg, usually 3 mg, Acute treatment 	<ul style="list-style-type: none"> BZD can be used as concomitant treatment until the onset of effect of the antidepressant. 	<ul style="list-style-type: none"> In general, BZDs should only be used in the acute phase of treatment (i.e. the first 4-6 weeks). Long-term use may be indicated if other drugs or CBT are ineffective or

Table 7: Summary of Recommendations for Benzodiazepine Use in GAD

Guideline/ Author, Year, Country	Benzodiazepine(s)	Treatment	Dose, Duration	Recommendations	Author's Additional Notes
			(4-8 weeks)		<p>not tolerated – mainly in rare cases.</p> <ul style="list-style-type: none"> Patients with a history of substance abuse should not take BZD. BZDs have little to no effect on depressive symptoms often accompanying GAD.
NICE, ¹² 2011, UK	Class; no specifics provided.	Primary or secondary care	NR	<ul style="list-style-type: none"> BZDs should only be offered in primary and secondary care as a short-term measure during crisis and prescribing should follow the advice in the British national formulary. 	<ul style="list-style-type: none"> Discuss options/concerns regarding treatments prior to prescribing, including benefits, side effects/withdrawal symptoms/drug interactions, importance to taking meds as prescribed, and the need to take after remission to avoid relapse.
CPA, ⁶ 2006, Canada	Alprazolam Bromazepam Diazepam Lorazepam	Second-line	NR for GAD ^c		<ul style="list-style-type: none"> Doses are provided (see Appendix 5, Table 5) for initial and maximum daily doses for healthy adults and not necessarily those with anxiety disorders. <p>Specific to Pregnancy (not necessarily for GAD):</p> <ul style="list-style-type: none"> BZDs can be used with caution in the first trimester of pregnancy and high doses should be used with caution in the third trimester and during labour and delivery. <p>Specific to BZDs:</p> <ul style="list-style-type: none"> BZD primarily relieve somatic symptoms and do not affect the key psychic features such as the ruminant

Table 7: Summary of Recommendations for Benzodiazepine Use in GAD

Guideline/ Author, Year, Country	Benzodiazepine(s)	Treatment	Dose, Duration	Recommendations	Author`s Additional Notes
					<p>worry.</p> <ul style="list-style-type: none"> BZDs are generally recommended for short-term use due to their side effect (i.e. sedation, cognitive impairment, and ataxia), withdrawal, and dependency issues. Some patients will require long-term adjunctive treatment with BZDs. Long-term use of BZDs may be indicated if there is no evidence of abuse, detrimental side effects, or misuse. <p>Specific to Children (not necessarily for GAD):</p> <ul style="list-style-type: none"> BZDs have not been well studied in children or adolescents. Children may be more prone to disinhibition and aggression with BZD use. Should be used sparingly in youths due to potential for dependency and abuse. Short-term use may be indicated in situations that cause high anxiety or while waiting for the effects of an antidepressant.

Table 7: Summary of Recommendations for Benzodiazepine Use in GAD

Guideline/ Author, Year, Country	Benzodiazepine(s)	Treatment	Dose, Duration	Recommendations	Author's Additional Notes
					<p>Specific to GAD:</p> <ul style="list-style-type: none"> Patients who have an inadequate response to optimal dosages of first line medications (SSRI) in the first 8-12 weeks should switch to another 1st-line medication (SSRI) or one with a different mechanism of action (SNRI) before trying a 2nd-line medication (BZD). BZD may be used at any time during times when anxiety or agitation is severe. BZD should be used as a short-term treatment. <p>Specific to the Elderly (not necessarily for GAD):</p> <ul style="list-style-type: none"> Elderly patients more sensitive to both therapeutic and toxic effects of BZDs: therefore, they should be used in low dosages or avoided. Older patients may experience impaired cognitive function, daytime sedation, increased risk of falls, and dependence and withdrawal issues. The potential for drug interactions needs to be assessed.

Table 7: Summary of Recommendations for Benzodiazepine Use in GAD

Guideline/ Author, Year, Country	Benzodiazepine(s)	Treatment	Dose, Duration	Recommendations	Author`s Additional Notes
					<ul style="list-style-type: none"> Initial doses should be lower and any increases should be individualized and slow.

BAP = British Association for Psychopharmacology; BZD = benzodiazepine; CBT = cognitive behavioural therapy; GAD = Generalized Anxiety Disorder; NICE = National Institute for Health and Clinical Excellence; NR = not reported; SNRI = selective norepinephrine/noradrenaline reuptake inhibitors; SSRI = selective serotonin reuptake inhibitors; UK = United Kingdom.

^a Only one specified in recommendation; however, studies included other benzodiazepines such as diazepam, lorazepam, and bromazepam. The additional notes refer to the benzodiazepine class rather than an individual drug.

^b At least three previous treatments (such as after SSRIs, SNRIs, and a psychological intervention).

^c Initial and maximum Health Canada-approved daily doses are for healthy adults and not necessarily for those with anxiety disorders.